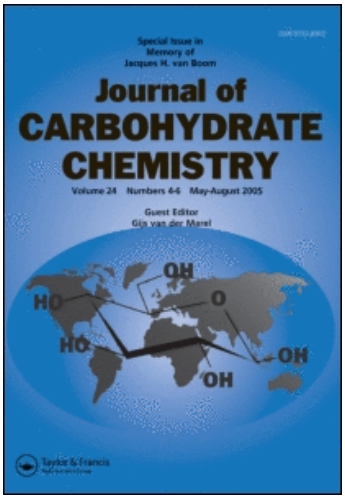

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Synthesis and Antiviral Evaluation of Some 5-*N*-Arylaminomethyl-2-glycosylsulphanyl-1,3,4-oxadiazoles and Their Analogs against Hepatitis A and Herpes Simplex Viruses

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Synthesis and Antiviral Evaluation of Some 5-*N*-Arylaminomethyl-2-glycosylsulphanyl-1,3,4-oxadiazoles and Their Analogs against Hepatitis A and Herpes Simplex Viruses

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N-Arylaminomethyl-3*H*-1,3,4-oxadiazole-2-thiones **2a**,**b** were prepared from the corresponding *N*-arylglycinoylhydrazides. A number of their thioglycoside derivatives **4**–**7a**–**c** and *S*-functionalized analogs **8**–**11a**,**b** were synthesized by the reaction with different acetobromosugars and acyclic hydroxyalkylating agents. The antiviral activity of a number of the synthesized compounds against herpes simplex virus type 1 (HSV-1) and hepatitis A virus (HAV) was evaluated. Compounds **5a** and **5b** showed promising results against HAV.

Keywords Thioglycosides, Oxadiazole, *S*-Functionalized-oxadiazole, Glycinoyl hydrazine, Antiviral activity, Herpes simplex virus type 1 (HSV-1), Hepatitis A virus (HAV)

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INTRODUCTION

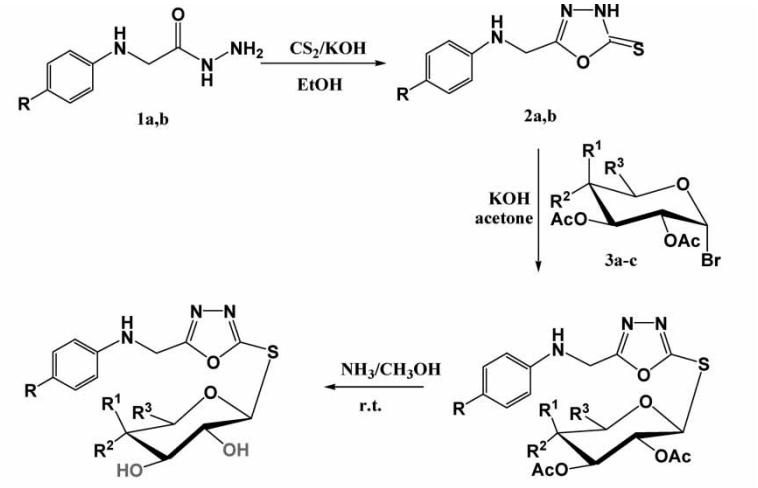
The high-throughput synthesis and screening of compound libraries have emerged as a key objective within the pharmaceutical industry to get new leads of potent biological activity. The 1,3,4-oxadiazole ring has been found in the skeleton of fungicidal and bactericidal, analgetic, antipyretic, antiphlogistic, anticompulsive, and paralytic hypnotic and sedative agents,[1–4] in addition to having antiviral activity[5] and a tyrosinase inhibiting effect.[6] On the other hand, the glycosylthio heterocycles[7–10] and the acyclicnucleoside[10–13] analogs including modifications of both the glycon and aglycon parts have stimulated extensive research as biological inhibitors.[14–18] Recently, we became interested in the synthesis of thioglycosides, compounds of potential biological activity, in addition to their use as glycosyl donors and/or acceptors.[10,18–20] Consequently, we have considered the attachment of 1,3,4-oxadiazoles, functionalized with arylmethylamino groups, to sugar moieties or open chain analogs to produce their respective thioglycosides and their acyclic analogs and evaluating their antiviral activity.

RESULTS AND DISCUSSION

Heterocyclization of the hydrazides **1a**,**b** with carbon disulfide in alkali gave 5-*N*-arylaminomethyl-3H-1,3,4-oxadiazole-2-thiones **2a**,**b**. Reaction of **2a**,**b** with acetobromo sugars in the presence of potassium hydroxide gave 5-*N*-arylaminomethyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-galactopyranosyl)sulphan-yl-1,3,4-oxadiazole, 5-*N*-arylaminomethyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)sulphanyl-1,3,4-oxadiazole, or 5-*N*-arylamino-methyl-2-(2′,3′,4′-tri-*O*-acetyl-*β*-D-xylopyranosyl)sulphanyl-1,3,4-oxadiazole **4a**–**c** and **5a**–**c**. The respective ^{1}H NMR spectra showed the anomeric proton of the sugar moiety in the range δ 5.40 to 5.78 ppm as doublet, with a coupling constant equal to 6.5 to 9.5 Hz indicating the *β*-orientation of the thioglycosidic bond. The anomeric proton of *β*-*N*-glucosides having an adjacent C═S was reported[21–26] to appear at higher chemical shift (δ 6.9–7.2 ppm) due to the anisotropic deshielding effect of the C═S.[22–26] The ^{13}C NMR spectrum of **5b** showed a signal at δ 78.11 corresponding to the anomeric C-1′, which also confirmed the *β*-configuration. The absence of a peak corresponding to the C═S group indicates that the attachment of the sugar has taken place at the sulfur atom and not on the nitrogen atom. This also agreed with the mode of their preparation.

When compounds **4a**–**c** and **5a**–**c** were treated with methanolic ammonia at 0°C, the deacetylated thioglycoside derivatives 5-*N*-arylaminomethyl-2-(*β*-D-glycopyranosyl)sulphanyl-1,3,4-oxadiazoles **6a**–**c** and **7a**–**c** were obtained in moderate yields (Sch. 1).

Compounds **2a**,**b** have been reacted with different acyclic oxygenated alkyl halides to give a series of open chain analogs of 1,3,4-oxadiazole. Reaction of the



Compound	R	R^1	R^2	R^3
6a	H	OH	H	CH_2OH
6b	H	H	OH	CH_2OH
6c	H	H	OH	H
7a	CH_3	OH	H	CH_2OH
7b	CH_3	H	OH	CH_2OH
7c	CH_3	H	OH	H

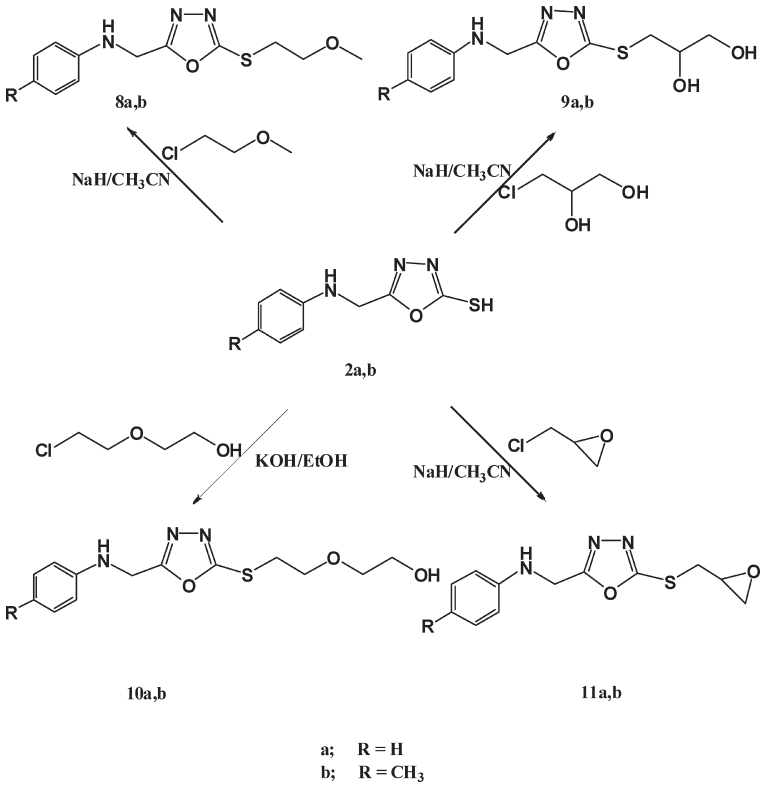
Compound	R	R^1	R^2	R^3
4a	H	OAc	H	CH_2OAc
4b	H	H	OAc	CH_2OAc
4c	H	H	OAc	H
5a	CH_3	OAc	H	CH_2OAc
5b	CH_3	H	OAc	CH_2OAc
5c	CH_3	H	OAc	H

Scheme 1

oxadiazole thiones **2a**,**b** with chloroethyl methyl ether and 3-chloropropan-1,2-diol in the presence of sodium hydride in anhydrous acetonitrile gave 5-*N*-arylaminomethyl-2-(2-methoxyethyl)sulphanyl-1,3,4-oxadiazole **8a**,**b** and 5-*N*-arylaminomethyl-2-(1,2-dihydroxypropyl)-sulphanyl-1,3,4-oxadiazoles **9a**,**b**. When the oxadiazole thiones **2a**,**b** were reacted with 2-(2-chloroethoxy)ethanol in absolute ethanol and in the presence of potassium hydroxide, the corresponding 5-*N*-arylaminomethyl-2-(2-hydroxyethoxyethyl)sulphanyl-1,3,4-oxadiazoles **10a**,**b** were obtained in 78% yield.

Reaction of the oxadiazole thiones **2a**,**b** with epichlorohydrine in anhydrous acetonitrile gave the corresponding 5-*N*-arylaminomethyl-2-[(oxiran-2-yl)methylsulphanyl]-1,3,4-oxadiazoles **11a**,**b** (Sch. 2).

Plaque infectivity assay was carried out to test a number of selected compounds for their antiviral activity. The test was performed to include three possibilities for antiviral activity: virucidal effect, virus adsorption, and effect on virus replication for both hepatitis A virus (HAV) and herpes simplex virus



Scheme 2

type 1 (HSV-1). The antiviral activity against HAV revealed that compounds **5a** and **5b** showed the highest activity at concentration 20 $\mu g/10^5$, whereas compounds **4b** showed little activity (Fig. 1). The activity of **5a** and **5b** has been found to be even higher than that of the standard amantadine. These data may indicate that there is not much difference between the gluco- and galacto- analogs, but both are characterized by the presence of a constituent

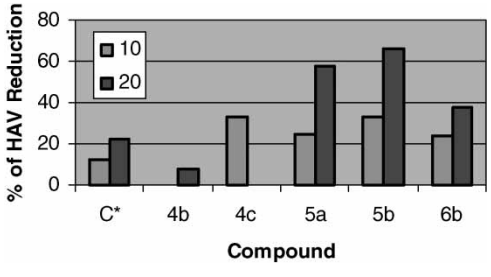


Figure 1: Effect of some novel compounds on hepatitis A virus (HAV) reduction in comparison with amantadine (C*) as a control.

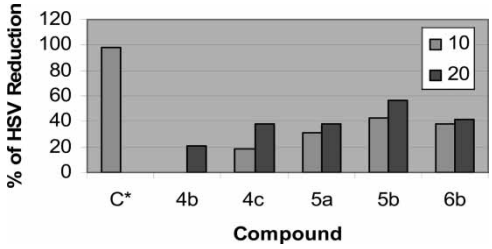


Figure 2: Effect of some novel compounds on herpes simplex virus-1 (HSV-1) reduction in comparison with acyclovir (C*) as a control.

on the aromatic ring. On the other hand, the activity against HSV-1 indicated that compound **5b** showed the highest activity, while compounds **4c** and **4b** showed little activity at concentrations of 10 and 20 $\mu g/10^5$ (Fig. 2), but all have less activity than the standard acyclovir.

In conclusion, a series of glycosylsulphanyl-oxadiazoles has been prepared. The biological activity studies indicated that compounds **5a** and **5b** are promising candidates against HAV.

EXPERIMENTAL

Melting points were determined with a Kofler block apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer model 1720 FTIR spectrometer for KBr disc. NMR spectra were recorded on a Varian Gemini 200 NMR Spectrometer at 300 MHz for ^1H and at 75 MHz for ^{13}C or on a Brucker Ac-250 FT spectrometer at 250 MHz for ^1H and at 62.9 MHz for ^{13}C. Chemical shifts were reported in δ scale (ppm) relative to TMS as a standard and the coupling constants J values are given in Hz. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F_{245}. The starting *N*-arylglycinoylhdrazides were prepared according to a literature method.[27] Elemental analyses were performed at the Microanalytical Data Centre at Faculty of Science, Cairo University, Egypt. Viral screening against HAV and HSV was conducted at the Environmental Virology Lab, Department of Water Pollution Research, National Research Centre, Cairo, Egypt.

5-*N*-Arylaminomethyl-3H-1,3,4-oxadiazole-2-thione (2a,b)

General Procedure

To a solution of *N*-arylglycinoylhydrazide **1a**,**b** (0.02 mol) in ethanol (50 mL) was added a solution of potassium hydroxide (0.02 mol) in water (2 mL) and carbon disulphide (5 mL). The solution was heated under reflux

for 15 h. The solvent was evaporated and the residue was dissolved in water, filtered, and acidified with dilute hydrochloric acid. The precipitate was filtered off, washed with water, and crystallized from ethanol.

5-*N*-Phenylaminomethyl-3H-1,3,4-oxadiazole-2-thione (2a)

Yield 78%; m.p. 157–159°C; IR (KBr): 3315 (NH), 1615 cm^{-1} (C═N). ^1H NMR (DMSO-d_6, 300 MHz): δ 4.38 (d, 2H, $J = 5.4$ Hz, CH_2), 5.65 (t, 1H, $J = 5.4$ Hz, NH), 6.61 (m, 3H, Ar-3H), 7.07 (m, 2H, Ar-2H), 11.22 (s, 1H, NH). Analysis calcd. for $C_9H_9N_3OS$: C, 52.16; H, 4.38; N, 20.27. Found: C, 51.82; H, 4.77; N, 19.98%.

5-*N*-(4-Tolyl)aminomethyl-3H-1,3,4-oxadiazole-2-thione (2b)

Yield 81%; m.p. 155–156°C; IR (KBr): 3344 (NH), 1610 cm^{-1} (C═N). ^1H NMR (DMSO-d_6, 300 MHz): δ 2.14 (s, 3H, CH_3), 4.24 (d, 2H, $J = 5.4$ Hz, CH_2), 5.60 (t, 1H, $J = 5.4$ Hz, NH), 6.55 (d, 2H, $J = 8.5$ Hz, Ar-2H), 6.95 (d, 2H, $J = 8.5$ Hz, Ar-2H), 14.24 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 19.96 (CH_3), 38.04 (CH_2), 112.44 (C-3,5), 125.40 (ArC-4), 129.32 (ArC-2,6), 144.87 (ArC-1), 162.43 (C═N), 177.76 (C═S). Analysis calcd. for $C_{10}H_{11}N_3OS$: C, 54.28; H, 5.01, N, 18.99. Found: C, 54.66; H, 5.16; N, 18.70%.

5-*N*-Arylaminomethyl-2-(per-*O*-acetyl-β-D-glycopyranosyl)sulphanyl-1,3,4-oxadiazoles (4–5a,b)

General Procedure

To a solution of the appropriate thiol **2a,b** (0.01 mol) in aqueous potassium hydroxide [0.01 mol in distilled water (16 mL)] was added a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-galacto **(3a)** or gluco- **(3b)** pyranosyl bromide and/or 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide **(3c)** (0.01 mol) in acetone (30 mL). The reaction mixture was stirred at rt until reaction was judged complete by TLC using chloroform/methanol 99.5:0.5. The solvent was evaporated under reduced pressure at 40°C and the residue was washed with distilled water to remove potassium bromide formed. The product was dried and crystallized from ethanol.

5-*N*-Phenylaminomethyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranos-yl)sulfanyl-1,3,4-oxadiazole (4a)

Yield 76%; m.p. 136–137°C; IR (KBr): 3296 (NH), 1753 cm^{-1} (C═O). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.98, 2.03, 2.15, 2.23 (4s, 12H, 4 CH_3), 4.11 (dd, 1H, $J = 10.2$ Hz, $J = 3.5$ Hz, H-5′), 4.14 (d, 2H, $J = 5.4$ Hz, CH_2), 4.15 (dd,

1H, $J = 3.8$, 10.2 Hz, H-6″), 4.48 (dd, 1H, $J = 11.3$, 3.8 Hz, H-6′), 5.10 (t, 1H, $J = 3.2$ Hz, H-4′), 5.18 (dd, 1H, $J = 6.6$, 3.2 Hz, H-3′), 5.29 (t, 1H, $J = 6.6$ Hz, H-2′), 5.51 (d, 1H, $J = 8.5$ Hz, H-1′), 5.66 (t, 1H, $J = 5.4$ Hz, NH), 6.60 (m, 3H, Ar-3H), 7.05 (m, 2H, Ar-2H). Analysis calcd. for $C_{23}H_{27}N_3O_{10}S$: C, 51.39; H, 5.06; N, 7.82. Found: C, 51.20; H, 4.95; N, 7.71%.

5-*N*-Phenylaminomethyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranos-yl)sulphanyl-1,3,4-oxadiazole (4b)

Yield 76%; m.p. 135–137°C; IR (KBr): 3320 (NH), 1749 cm^{-1} (C═O). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.99, 2.01, 2.05, 2.06 (4s, 12H, 4 CH_3), 3.95 (m, 1H, H-5′), 4.12 (dd, 1H, $J = 10.4$, 3.3 Hz, H-6″), 4.23 (dd, 1H, $J = 10.8$, 3.2 Hz, H-6′), 4.26 (d, 2H, $J = 5.4$ Hz, CH_2), 5.08 (dd, 1H, $J = 6.5$ Hz, $J = 2.8$ Hz, H-4′), 5.26 (dd, 1H, $J = 2.8$, 5.8 Hz, H-3′), 5.31 (t, 1H, $J = 5.8$ Hz, H-2′), 5.65 (t, 1H, $J = 5.4$ Hz, NH), 5.79 (d, 1H, $J = 8.8$ Hz, H-1′), 6.62 (m, 3H, Ar-3H), 7.16 (m, 2H, Ar-2H). Analysis calcd. for $C_{23}H_{27}N_3O_{10}$ S: C, 51.39; H, 5.06; N, 7.82. Found: C, 51.09; H, 4.81; N, 8.20%.

5-*N*-Phenylaminomethyl-2-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl) sulphanyl-1,3,4-oxadiazole (4c)

Yield 76%; m.p. 142–144°C; IR (KBr): 3482 (NH), 1751 cm^{-1} (C═O). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.09, 2.11, 2.16 (3s, 9H, 3 CH_3), 4.17 (dd, 1H, $J = 9.8$, 3.2 Hz, H-5′), 4.22 (dd, 1H, $J = 10.4$, 3.4 Hz, H-5″), 4.36 (m, 1H, H-4′), 4.37 (d, 2H, $J = 5.4$ Hz, CH_2), 4.88 (dd, 1H, $J = 6.5$, 3.8 Hz, H-3′), 5.22 (t, 1H, $J = 3.8$ Hz, H-2′), 5.60 (t, 1H, $J = 5.4$ Hz, NH), 5.76 (d, 1H, $J = 8.4$ Hz, H-1′), 6.66 (m, 3H, Ar-3H), 7.27 (m, 2H, Ar-2H). Analysis calcd. for $C_{20}H_{23}N_3O_8S$: C, 51.60; H, 4.98; N, 9.03. Found: C, 51.66; H, 4.64; N, 8.78%.

5-*N*-(4-Tolyl)aminomethyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyran-osyl)sulphanyl-1,3,4-oxadiazole (5a)

Yield 79%; m.p. 135–137°C; IR (KBr): 3391 (NH), 1747 cm^{-1} (C═O). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.97, 2.01, 2.05, 2.09, 2.24 (5s, 15H, 5 CH_3), 3.90 (dd, 2H, $J = 11.2$, 3.4 Hz, H-6′), 4.03 (dd, 1H, $J = 4.6$ Hz, $J = 11.2$ Hz, H-6″), 4.25 (m, 1H, H-5′), 4.55 (d, 2H, $J = 5.4$ Hz, CH_2), 5.08 (dd, 1H, $J = 6.8$, 2.6 Hz, H-4′), 5.26 (dd, 1H, $J = 2.6$, 5.8 Hz, H-3′), 5.29 (t, 2H, $J = 5.8$ Hz, H-2′), 5.40 (d, 1H, $J = 9.5$ Hz, H-1′), 5.68 (t, 1H, $J = 5.4$ Hz, NH), 6.60 (d, 2H, $J = 8.5$ Hz, Ar-2H), 7.05 (d, 2H, $J = 8.5$ Hz, Ar-2H). Analysis calcd. for C_{24} $H_{29}N_3O_{10}S$: C, 52.26; H, 5.30; N, 7.62. Found: C, 52.61; H, 5.39; N, 7.69%.

5-*N*-(4-Tolyl)aminomethyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranos-yl)sulphanyl-1,3,4-oxadiazole (5b)

Yield 78%; m.p. 130–141°C; IR (KBr): 3398 (NH), 1753 cm^{-1} (C═O). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.84, 1.99, 2.06, 2.09, 2.25 (5s, 15H, 5 CH_3), 3.90 (m, 1H, H-5′), 4.13 (dd, 1H, $J = 10.5$, 3.4 Hz, H-6″), 4.28 (dd, 1H, $J = 10.5$, 3.4 Hz, H-6′), 4.45 (d, 2H, $J = 5.4$ Hz, CH_2), 4.95 (m, 1H, H-4′), 5.36 (dd, 1H, $J = 6.5$, 3.2 Hz, H-3′), 5.58 (t, 1H, $J = 6.5$ Hz, H-2′), 5.65 (t, 1H, $J = 5.4$ Hz, NH), 5.78 (d, 1H, $J = 9.2$ Hz, H-1′), 6.58 (d, 2H, $J = 8.5$ Hz, Ar-2H), 7.05 (d, 2H, $J = 8.5$ Hz, Ar-2H). ^{13}C NMR ($CDCl_3$): δ 15.19, 15.25, 15.35, 15.38, 15.49 ($5CH_3$), 34.2 (CH_2), 62.85 (C-6′), 64.57 (C-5′), 68.39 (C-4′), 71.27 (C-3′), 71.44 (C-2′), 78.11 (C-1′), 108.25 (ArC-2,6), 116.36 (ArC-4), 124.76 (ArC-3,5), 138.71 (ArC-l), 156.17 (C═N), 161.63 (C═N), 164.12, 164.21, 164.73, 165.35 (4CO). Analysis calcd. for $C_{24}H_{29}N_3O_{10}S$: C, 52.26; H, 5.30; N, 7.62. Found: C, 52.12; H, 5.14: N, 7.39%.

5-*N*-(4-Tolyl)aminomethyl-2-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)sulphanyl-1,3,4-oxadiazole (5c)

Yield 78%; m.p. 137–139°C; IR (KBr): 3420 (NH), 1750 cm^{-1} (C═O). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.06, 2.08, 2.24, 2.23 (4s, 12H, 4 CH_3), 4.23 (dd, 1H, $J = 9.8$, 2.6 Hz, H-5′), 4.27 (dd, 1H, $J = 10.2$, 2.8 Hz, H-5″), 4.55 (d, 2H, $J = 5.4$ Hz, CH_2), 4.91 (m, 1H, H-4′), 5.08 (t, 1H, $J = 4.2$ Hz, H-3′), 5.19 (dd, 1H, $J = 6.5$, 4.2 Hz, H-2′), 5.62 (d, 1H, $J = 8.5$ Hz, H-1′), 5.70 (t, 1H, $J = 5.4$ Hz, NH), 6.60 (d, 2H, $J = 8.5$ Hz, Ar-2H), 7.05 (d, 2H, $J = 8.5$ Hz, Ar-2H). Analysis calcd. for $C_{21}H_{25}N_3O_8$ S: C, 52.60; H, 5.26; N, 8.76. Found: C, 52.31; H, 5.53; N, 8.53%.

5-*N*-Arylaminomethyl-2-((β-D-glycopyranosyl))sulphanyl-1,3,4-oxadiazoles (6–7a–c)

General Procedure

Dry gaseous ammonia was passed through a solution of a protected nucleoside **4–5a–c** (0.5 g) in dry methanol (20 mL) at 0°C for 0.5 h, and then the mixture was stirred at 0°C for about 5 h. The solvent was evaporated under reduced pressure at 40°C to give a solid residue, which was crystallized from ethanol.

5-*N*-Phenylaminomethyl-2-(β-D-galactopyranosyl)sulphanyl-1,3,4-oxadiazole (6a)

Yield 69%; m.p. 182–183°C; IR (KBr): 3490–3446 (OH), 3288 cm^{-1} (NH). ^1H NMR (DMSO-d_6, 300 MHz): δ 3.38 (m, 1H, H-6′), 4.41 (dd, 1H, $J = 10.2$,

2.2 Hz, H-6″), 3.62 (m, 1H, H-5′), 3.64 (m, 1H, H-4′), 4.04 (t, 1H, $J = 4.8$ Hz, H-3′), 4.13 (dd, 1H, $J = 8.2$, 4.8 Hz, H-2′), 4.35 (m, 1H, OH), 4.36 (d, 2H, $J = 5.4$ Hz, CH_2), 4.92 (d, 1H, $J = 4.5$ Hz, OH), 5.13 (d, 1H, $J = 4.5$ Hz, OH), 5.57 (t, 1H, $J = 4.2$ Hz, OH), 5.75 (t, 1H, $J = 5.4$ Hz, NH), 5.81 (d, 1H, $J = 8.2$ Hz, H-1′), 6.56 (m, 3H, Ar-3H), 7.06 (m, 2H, Ar-2H). Analysis calcd. for $C_{15}H_{19}N_3O_6S$: C, 48.76; H, 5.19; N, 11.38. Found: C, 48.51; H, 5.03; N, 11.25%.

5-*N*-Phenylaminomethyl-2-(β-D-glucopyranosyl)sulfanyl-1,3,4-oxadiazole (6b)

Yield 70%; m.p. 177–178°C; IR (KBr): 3350–3400 (OH), 3220 cm^{-1} (NH). ^1H NMR (DMSO-d_6, 300 MHz): δ 3.42 (m, 1H, H-6′), 3.54 (dd, 1H, $J = 10.4$, 2.8 Hz, H-6″), 3.65 (m, 1H, H-5′), 3.94 (m, 1H, H-4′), 4.16 (t, 1H, $J = 3.8$ Hz, H-3′), 4.24 (d, 2H, $J = 5.4$ Hz, CH_2), 4.53 (t, 1H, $J = 8.4$ Hz, H-2′), 4.77 (d, 1H, $J = 4.5$ Hz, OH), 4.88 (dd, 1H, $J = 5.2$, 2.4 Hz, OH), 5.07 (t, 1H, $J = 5.2$ Hz, OH), 5.44 (d, 1H, $J = 2.4$ Hz, OH), 5.68 (t, 1H, $J = 5.4$ Hz, NH), 5.73 (d, 1H, $J = 8.4$ Hz, H-1′), 6.01 (t, 1H, $J = 5.4$ Hz, NH), 6.58 (m, 3H, Ar-3H), 6.92 (m, 2H, Ar-2H). Analysis calcd. for $C_{15}H_{19}N_3O_6S$: C, 48.76; H, 5.19; N, 11.38%. Found: C, 48.69; H, 5.21; N, 11.31%.

5-*N*-Phenylaminomethyl-2-(β-D-xylopyranosyl)sulfanyl-1,3,4-oxadiazole (6c)

Yield 68%; m.p. 183–185°C; IR (KBr): 3335–3420 (OH), 3195 cm^{-1} (NH). ^1H NMR (DMSO-d_6, 300 MHz): δ 3.62 (m, 2H, H-5′, H-5″), 3.69 (dd, 1H, $J = 6.4$, 2.4 Hz, H-4′), 4.80 (m, 1H, H-3′), 4.04 (d, 2H, $J = 5.4$ Hz, CH_2), 5.26 (dd, 1H, $J = 6.5$, 2.4 Hz, H-2′), 4.95 (m, 1H, OH), 5.38 (m, 2H, 2OH), 5.65 (t, 1H, $J = 5.4$ Hz, NH), 5.70 (d, 1H, $J = 6.5$ Hz, H-1′), 6.21 (t, 1H, $J = 5.4$ Hz, NH), 6.62 (m, 3H, Ar-3H), 7.35 (m, 2H, Ar-2H). Analysis calcd. for $C_{14}H_{17}N_3O_5S$: C, 49.54; H, 5.05; N, 12.38. Found: C, 49.65; H, 5.16; N, 12.42%.

5-*N*-(4-Tolyl)aminomethyl-2-(β-D-galactopyranosyl)sulfanyl-1,3,4-oxadiazole (7a)

Yield 72%; m.p. 179–181°C; IR (KBr): 3315–3390 (OH), 3220 cm^{-1} (NH). Analysis calcd. for $C_{16}H_{21}N_3O_6S$: C, 50.11; H, 5.52; N, 10.96. Found: C, 50.09; H, 5.48; N, 10.59%.

5-*N*-(4-Tolyl)aminomethyl-2-(β-D-glucopyranosyl)sulfanyl-1,3,4-oxadiazole (7b)

Yield 71%; m.p. 187–189°C; IR (KBr): 3380–3410 (OH), 3255 cm^{-1} (NH). Analysis calcd. for $C_{16}H_{21}N_3O_6S$: C, 50.11; H, 5.52; N, 10.96. Found: C, 49.88; H, 5.38; N, 10.78%.

5-*N*-(4-Tolyl)aminomethyl-2-(β-D-xylopyranosyl)sulfanyl-1,3,4-oxadiazole (7c)

Yield 70%; m.p. 182–184°C; IR (KBr): 3390–3450 (OH), 3305 cm^{-1} (NH). ^1H NMR (DMSO-d_6, 300 MHz): δ 2.14 (s, 3H, CH_3), 3.54 (m, 1H, H-5′), 3.57 (dd, 1H, $J = 9.5$, 3.2 Hz, H-5″), 3.65 (dd, 1H, $J = 3.2$, 6.8 Hz, H-4′), 3.81 (dd, 1H, $J = 6.8$, 2.4 Hz, H-3′), 4.03 (t, 1H, $J = 6.8$ Hz, H-2′), 4.35 (d, 2H, $J = 5.4$ Hz, CH_2), 4.89 (m, 1H, OH), 5.46 (m, 2H, 2OH), 5.88 (d, 1H, $J = 6.8$ Hz, H-1′), 6.11 (t, 1H, $J = 5.4$ Hz, NH), 6.54 (d, 2H, $J = 8.5$ Hz, Ar-2H), 6.93 (d, 2H, $J = 8.5$ Hz, Ar-2H). Analysis calcd. for $C_{15}H_{19}N_3O_5S$: C, 50.97; H, 5.42; N, 11.89. Found: C, 50.65; H, 5.12; N, 11.81%.

5-*N*-Arylaminomethyl-2-(2-methoxyethyl)sulfanyl-1,3,4-oxadiazole (8a,b)

A mixture of 5-*N*-arylaminomethyl-1,3,4-oxadiazole-2-thiones **2a**,**b** (0.01 mol) and sodium hydride (0.01 mol) in anhydrous acetonitrile was stirred for 2 h. The reaction mixture was cooled to 0°C and chloroethylmethyl ether (0.01 mol) was added. The mixture was stirred for 8 h, the solid precipitate was filtered, and the filtrate was removed under reduced pressure. The residue was purified on silica gel column chromatography using chloroform/methanol (95:5) to give **8a**,**b**.

5-*N*-Phenylaminomethyl-2-(2-methoxyethyl)thio-1,3,4-oxadiazole (8a)

Yield 72%; IR (KBr): 3329 (NH), 1612 cm^{-1} (C=N). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.35 (s, 3H, OCH_3), 3.36 (t, 2H, $J = 4.5$ Hz, CH_2), 3.70 (t, 2H, $J = 4.5$ Hz, CH_2), 4.55 (d, 2H, $J = 5.4$ Hz, CH_2), 5.70 (t, 1H, $J = 5.4$ Hz, NH), 6.75 (m, 3H, Ar-3H), 7.35 (m, 2H, Ar-2H). Analysis calcd. for $C_{12}H_{15}N_3O_2S$: C, 54.32; H, 5.70, N, 15.84. Found: C, 54.12; H, 5.36; N, 15.71%.

5-*N*-(4-Tolyl)aminomethyl-2-(2-methoxyethyl)sulfanyl-1,3,4-oxadiazole (8b)

Yield 77%; IR (KBr): 3281 (NH), 1615 cm^{-1} (C=N). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.25 (s, 3H, CH_3), 3.35 (s, 3H, OCH_3), 3.40 (t, 2H, $J = 4.5$ Hz, CH_2), 3.70 (t, 2 H, $J = 4.5$ Hz, CH_2), 4.55 (d, 2H, $J = 5.4$ Hz, CH_2), 5.45 (t, 1H, $J = 5.4$ Hz, NH), 6.55 (d, 2H, $J = 8.5$ Hz, Ar-2H), 7.05 (d, 2H, $J = 8.5$ Hz, Ar-2H). Analysis calcd. for $C_{13}H_{17}N_3O_2S$: C, 55.89; H, 6.13, N, 15.04. Found: C, 55.52; H, 5.95; N, 14.70%.

5-*N*-Arylaminomethyl-2-((1,2-dihydroxypropyl)sulfanyl)-1,3,4-oxadiazole (9a,b)

A mixture of 5-*N*-arylaminomethyl-1,3,4-oxadiazole-2-thiones **2a**,**b** (0.01 mol) and sodium hydride (0.01 mol) in dry acetonitrile was stirred for 2 h. The reaction mixture was cooled to 0°C and 3-chloropropan-1,2-diol (0.01 mol) was added. The mixture was stirred for 6 h, and the solid precipitate was filtered off. The filtrate was evaporated under reduced pressure. The residue was purified on silica gel column chromatography using chloroform/methanol (95:5) as mobile phase to give **9a**,**b**.

5-*N*-Phenylaminomethyl-2-(1,2-dihydroxypropyl)sulfanyl)-1,3,4-oxadiazole (9a)

Yield 78%; IR (KBr): 3328 (OH), 3250 cm^{-1} (NH). ^1H NMR (DMSO-d_6, 300 MHz): δ 3.48 (m, 2H, CH_2), 3.64 (d, 2H, $J = 4.5$ Hz, CH_2), 3.78 (d, 2H, $J = 5.4$ Hz, CH_2), 3.60 (m, 1H, CH), 4.19 (t, 1H, $J = 4.2$ Hz, OH), 4.49 (d, 1 H, $J = 3.8$ Hz, OH), 5.55 (t, 1H, $J = 5.4$ Hz, NH), 6.62 (m, 3H, Ar-3H), 7.11 (m 2H, Ar-2H). Analysis calcd. for $C_{12}H_{15}N_3O_3S$: C, 51.23; H, 5.73, N, 14.94. Found: C, 51.66; H, 5.40; N, 15.16%.

5-*N*-(4-Tolyl)aminomethyl-2-((1,2-dihydroxypropyl)sulfanyl)-1,3,4-oxadiazole (9b)

Yield 80%; IR (KBr): 3393 (OH), 3319 cm^{-1} (NH). ^1H NMR (DMSO-d_6, 300 MHz): δ 2.20 (s, 3H, CH_3), 3.54 (m, 2H, CH_2), 3.56 (d, 2H, $J = 4.5$ Hz, CH_2), 3.60 (m, 1H, CH), 3.89 (d, 2H, $J = 5.4$ Hz, CH_2) 3.91 (t, 1H, $J = 4.2$ Hz, OH), 4.48 (d, 1H, $J = 3.8$ Hz, OH), 5.60 (t, 1H, $J = 5.4$ Hz, NH), 6.58 (d, 2H, $J = 8.5$ Hz, Ar-2H), 6.97 (d, 2H, $J = 8.5$ Hz, Ar-2H). Analysis calcd. for $C_{13}H_{17}N_3O_3S$: C, 52.86; H, 5.80, N, 14.23. Found: C, 52.66; H, 6.16; N, 13.86%.

5-*N*-Arylaminomethyl-2-((2-hydroxyethoxyethyl)sulfanyl)-1,3,4-oxadiazoles (10a,b)

A solution of 5-*N*-arylaminomethyl-1,3,4-oxadiazole-2-thiones **2a**,**b** (0.01 mol) and potassium hydroxide (0.01 mol) in ethanol (25 mL) was warmed until all potassium hydroxide was dissolved, and then 2-(2-chloroethoxy)ethanol (0.01 mol) was added. The reaction mixture was heated under reflux for 5 h. The resulting precipitate was filtered off, the solvent was removed under reduced pressure and the remained precipitate was washed and crystallized.

5-*N*-Phenylaminomethyl-2-((2-hydroxyethoxyethy)sulfanyl)-1,3,4-oxadiazole (10a)

Yield 79%; m.p. 167–169°C; yield 79%; IR (KBr): 3315 (OH), 3225 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.36 (m, 2H, CH_2), 3.53 (t, 2H, $J = 5.2$ Hz, CH_2) 3.67 (t, 2H, $J = 4.5$ Hz, CH_2), 3.71 (t, 2H, $J = 5.2$ Hz, CH_2), 4.35 (d, 2 H, $J = 5.4$ Hz, CH_2), 4.51 (t, $J = 4.4$ Hz, 1H, OH), 5.65 (t, 1H, $J = 5.4$ Hz, NH), 6.69 (m, 3H, Ar-3H), 7.13 (m, 2H, Ar-2H). Analysis calcd. for $C_{13}H_{17}N_3O_3S$: C, 52.86; H, 5.80, N, 14.23. Found: C, 53.11; H, 5.75; N, 14.49%.

5-*N*-(4-Tolyl)aminomethyl-2-((2-hydroxyethoxyethyl) sulfanyl)-1,3,4-oxadiazole (10b)

Yield 78%; m.p. 164–165°C; IR (KBr): 3359 (OH), 3190 cm^{-1} (NH). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.22 (s, 3H, CH_3), 3.40 (m, 2H, CH_2), 3.57 (t, 2H, $J = 5.2$ Hz, CH_2), 3.62 (t, 2H, $J = 4.4$ Hz, CH_2), 3.80 (t, 2H, $J = 5.2$ Hz, CH_2), 4.48 (d, 2H, $J = 5.4$ Hz, CH_2), 4.51 (t, 1H, $J = 4.4$ Hz, OH), 5.70 (t, 1H, $J = 5.4$ Hz, NH), 6.61 (d, 2H, $J = 8.5$ Hz, Ar-2H), 6.99 (d, 2H, $J = 8.5$ Hz, Ar-2H). Analysis calcd. for $C_{14}H_{19}N_3O_3S$: C, 54.35; H, 6.19; N, 13.58%. Found: C, 54.22; H, 5.85; N, 13.34%.

5-*N*-Arylaminomethyl-2-((oxiran-2-yl)methylsulfanyl)-1,3,4-oxadiazoles (11a,b)

A mixture of 5-*N*-arylaminomethyl-1,3,4-oxadiazole-2-thiones **2a**,**b** (0.01 mol) and sodium hydride (0.01 mol) in anhydrous acetonitrile was stirred for 2 h. The reaction mixture was cooled to 0°C and epichlorohydrine (0.01 mol) was added. The mixture was stirred for 6 h. at 60 to 70°C, the solid precipitate was filtered off and the filtrate was reduced under reduced pressure, and the formed precipitate was washed and recrystallized from ethanol.

5-*N*-Phenylaminomethyl-2-((oxiran-2-yl)methylsulfanyl)-1,3,4-oxadiazole (11a)

Yield 72%; m.p. 169–170°C; IR (KBr): 3325 (NH), 1605 (C=N) Analysis calcd. for $C_{25}H_{13}N_3O_2S$: C, 54.74; H, 4.98; N, 15.96. Found: C, 54.63; H, 4.92; N, 15.65%.

5-*N*-(4-Tolyl)aminomethyl-2-((oxiran-2-yl)methylsulfanyl)-1,3,4-oxadiazole (11b)

Yield 74%; m.p. 166–168°C; IR (KBr): 3320 (NH), 1610 cm^{-1} (C=N). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.22 (s, 3H, CH_3), 3.66 (d, 2H, $J = 5.8$ Hz,

CH_2), 3.82 (d, 2H, $J = 5.2$ Hz, CH_2), 4.22 (d, 2H, $J = 5.4$ Hz, CH_2), 4.55 (m, 1H, CH), 6.54 (d, 2H, $J = 8.5$ Hz, Ar-2H), 6.99 (d, 2H, $J = 8.5$ Hz, Ar-2H). Analysis calcd. for $C_{13}H_{17}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15. Found: C, 55.95; H, 5.21; N, 15.29%.

BIOLOGICAL ACTIVITY STUDIES

Preparation of Compounds for Bioassay

Tested compounds were dissolved as 100 mg each in 1 mL of 10% DMSO in water. The final concentration was 100 μg/μL (stock solution). The dissolved stock solutions were decontaminated by addition of 50 μg/mL antibiotic antimycotic mixture (10,000 U penicillin G sodium, 10,000 μg streptomycin sulfate, and 250 μg amphotericin B, PAA Laboratories GmbH, Austria).

Cell Culture

African green monkey kidney-derived cells (Vero) and human hepatoma cell line (HepG2) were used. Cells were propagated in Dulbecco's Minimal Essential Medium (DMEM) supplemented with 10% foetal bovine serum and 1% antibiotic-antimycotic mixture. The pH was adjusted at 7.2 to 7.4 by 7.5% sodium bicarbonate solution. The mixture was sterilized by filtration through 0.2-μm pore size nitrocellulose membrane.

Viruses

HSV-1 and HAV (MBB-cell culture adapted strain) were obtained from Environmental Virology Lab, Department of Water Pollution Research, National Research Centre, Cairo, Egypt.

Cytotoxicity Assay

Cytotoxicity was assayed for both dimethyl sulfoxide (DMSO) and the tested compounds. Serial dilutions were prepared and inoculated on Vero cells grown in 96-well tissue culture plates. The maximum tolerated concentration (MTC) for each compound was determined by both cell morphology and cell viability by staining with tryban blue dye.

Plaque Reduction Infectivity Assay

A 6-well plate was cultivated with cell culture (10^5 cell/mL) and incubated for 2 days at 37°C. HSV-1 and HAV were diluted to give 10^4 PFU/mL final concentrations for each virus and mixed with the tested compound at the previous concentration and incubated overnight at 4°C. Growth medium was removed

from the multiwell plate and virus-compound mixture was inoculated (100 μL/well). After 1 h contact time, the inoculum was aspirated and 3 mL of MEM with 1% agarose was overlaid on the cell sheets. The plates were left to solidify and incubated at 37°C until the development of virus plaques. Cell sheets were fixed in 10% formalin solution for 2 h and stained with crystal violet stain. Control virus and cells were treated identically without chemical compound. Virus plaques were counted and the percentage of reduction was calculated.[28]

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